PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PCB/PN/P89169PWO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB 03/03159	23.07.2003	24.07.2002
International Patent Classification (IPC) or both national classification and IPC		
A61K38/55, A61K38/55		
Applicant		
RENOVO LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14.01.2004	24.05.2004
Name and mailing address of the international preliminary examining authority:	Authorized Officer
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/03159

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-29 as originally filed

Claims, Numbers

1-13 received on 11.05.2004 with letter of 11.05.2004

Drawings, Sheets

1/4-4/4 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☒ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-13
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-13
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-13
	No:	Claims	

2. Citations and explanations

   see separate sheet

Concerning section V

1. The following documents are referred to; the numbering will be adhered to in the rest of the procedure:

D1: GB-A-2 324 960 (UNIV MANCHESTER) 11 November 1998 (1998-11-11)
D2: WO 95 02579 A (ZENECA LTD ;CRAWLEY GRAHAM CHARLES (GB)) 26 January 1995 (1995-01-26)
D3: US-B1-6 262 020 (LEZDEY JOHN ET AL) 17 July 2001 (2001-07-17)
D4: US-A-5 439 824 (BRANTLY MARK ET AL) 8 August 1995 (1995-08-08)
D5: EP-A-0 968 723 (UNIV MANCHESTER) 5 January 2000 (2000-01-05)
D6: SHARON O'KANE ET AL: 'Transforming Growth Factor betas and Wound Healing' INTERNATIONAL JOURNAL OF BIOCHEMISTRY AND CELL BIOLOGY, EXETER, GB, vol. 29, no. 1, 1997, pages 63-78, XP008018620 ISSN: 1357-2725
D7: DUBOIS C ET AL: 'Processing of transforming growth factor beta 1 precursor by human furin convertase' JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 270, no. 18, 5 May 1995 (1995-05-05), pages 10618-10624, XP002115939 ISSN: 0021-9258 cited in the application
D8: SHAH M ET AL: 'Neutralisation of TGF-beta 1 and TGF-beta 2 or exogenous addition of TGF-beta 3 to cutaneous rat wounds reduces scarring.' JOURNAL OF CELL SCIENCE. ENGLAND MAR 1995, vol. 108 (Pt 3), March 1995 (1995-03), pages 985-1002, XP002260292 ISSN: 0021-9533
D9: CAMERON A ET AL: 'Polyarginines Are Potent Furin Inhibitors' JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 275, no. 47, 24 November 2000 (2000-11-24), pages 36741-36749, XP002251991 ISSN: 0021-9258
D10: TOMLINSON ANNETTE ET AL: 'Wound healing: a model of dermal wound repair.' METHODS IN MOLECULAR BIOLOGY (CLIFTON, N.J.) UNITED STATES 2003, vol. 225, 2003, pages 249-260, XP001156105 ISSN: 1064-3745

Unless indicated otherwise reference is made to the relevant passages emphasized in the search report.

2. Novelty

D1, from the inventor of the present application, discloses the delivery of DNA encoding agents which neutralize a growth factor at a wound site, to inhibit scarring and fibrosis. Such agents are e.g. convertase (serine protease) inhibitors, which neutralize e.g. TGF-β1 or TGF-β2. D1 does not specify furin inhibitors among these agents.

D2 discloses the use of TNF convertase inhibitors for the treatment of TNF related diseases, e.g. pulmonary fibrosis or cirrhosis. D2 does not disclose the use of furin inhibitors.

D3 discloses the topical use of the convertase inhibitor alpha 1- antitrypsin for wound healing with prevention of scarring ; D4 discloses the topical (lung) use of a DNA molecule encoding AAT to treat e.g. cystic fibrosis.
It is not clear for the time being whether AAT is a furin inhibitor, hence the subject-matter of the present claims seems to be novel.
However, for the sake of clarity, the applicant should expect to be asked, when entering the national phase, to provide a statement that AAT is not a furin inhibitor, to indicate which inhibitors listed in the application are specific for furin, and to delete all other inhibitors from the application.
In addition, the applicant should be prepared to delete claim 2 as it renders the scope of claim 1 on which it depends unclear.

3. Inventive activity

The closest prior art is the document D5, from the inventor of the present application, which discloses the use of antibodies which diminish the activity of TGF-β1, for preventing scarring and fibrosis.

The inventors have now discovered that the convertase furin is responsible for the extracellular activation of platelet large latent TGF-β1 complex in the surrounding tissue following degranulation of platelets.
The difference over the closest prior art is the modulation of furin instead of a direct modulation of TGF-β1 by e.g. antibodies.
The problem is therefore to find an alternative way of preventing TGF-β1 activity, thereby preventing scarring or fibrosis.
The application solves the problem by the use of the furin inhibitors decanoyl-

RVKR-cmk or hexa-arginine.

It is known from the prior art that furin is responsible for the activation of pro-TGF-β1 (see D7). It is also known from the prior art that TGF-β1 and TGF-β2 but not TGF-β3 are responsible for scarring and fibrosis (see D6 and D8 from the inventor).
However, the discovery by the inventor that the furin inhibitor dec- RVKR-cmk reduces the generation of active TGF-β1 in vitro at the site of platelet activation could not be foreseen by the skilled person. Hence the subject-matter of the present claims seems to involve an inventive step.